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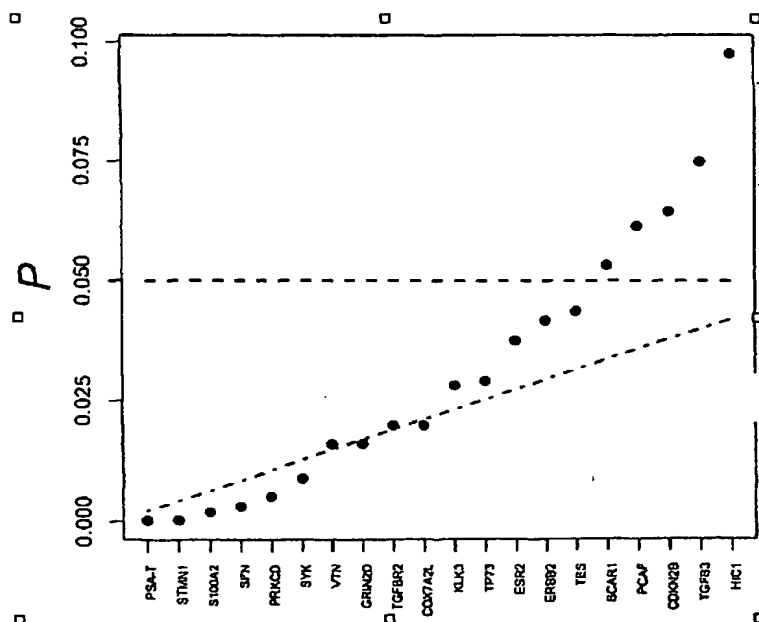
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[Continued on next page]

(54) Title: METHOD AND NUCLEIC ACIDS FOR THE TREATMENT OF BREAST CELL PROLIFERATIVE DISORDERS



(57) Abstract: The present invention relates to modified and genomic sequences, to oligonucleotides and/or PNA-oligomers for detecting the cytosine methylation state of genomic DNA, as well as to a method for predicting the response of a subject with a cell proliferative disorder of the breast tissues, to endocrine treatment.



(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10881

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/68912 A (PIEPENBROCK CHRISTIAN ; BERLIN KURT (DE); EPIGENOMICS AG (DE); OLEK AL) 20 September 2001 (2001-09-20) SEQ ID NO: 131 is a bisulphite-treated DNA corresponding to SEQ ID NO: 27 of the present application.claims 1-32	25-44, 78-80
Y	EP 1 167 975 A (UNIV PARIS DESCARTES) 2 January 2002 (2002-01-02) the whole document	1-24, 45-77

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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04. 08. 2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10881

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CURMI P A ET AL: "Overexpression of stathmin in breast carcinomas points out to highly proliferative tumours" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 82, no. 1, 2000, pages 142-150, XP002908452 ISSN: 0007-0920 the whole document	1-24, 45-77
A	----- WO 02/059347 A (UNIV JOHNS HOPKINS MED) 1 August 2002 (2002-08-01) the whole document examples 3,7; table 4	
A	----- BRATTSAND G: "Correlation of oncoprotein 18/stathmin expression in human breast cancer with established prognostic factors." BRITISH JOURNAL OF CANCER. AUG 2000, vol. 83, no. 3, August 2000 (2000-08), pages 311-318, XP002280240 ISSN: 0007-0920 the whole document	
A	----- LAPIDUS R G ET AL: "Methylation of estrogen and progesterone receptor gene 5' CpG islands correlates with lack of estrogen and progesterone receptor gene expression in breast tumors." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH. MAY 1996, vol. 2, no. 5, May 1996 (1996-05), pages 805-810, XP008030590 ISSN: 1078-0432 the whole document	
A	----- OTTAVIANO Y L ET AL: "Methylation of the estrogen receptor gene CpG island marks loss of estrogen receptor expression in human breast cancer cells" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 54, no. 10, 15 May 1994 (1994-05-15), pages 2552-2555, XP000999429 ISSN: 0008-5472 the whole document	
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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 03/10881

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HUANG TIM HUI-MING ET AL: "Methylation profiling of CpG islands in human breast cancer cells" HUMAN MOLECULAR GENETICS, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 8, no. 3, March 1999 (1999-03), pages 459-470, XP002175857 ISSN: 0964-6906 the whole document</p> <p>-----</p>	
A	<p>YAN P S ET AL: "Dissecting complex epigenetic alterations in breast cancer using CpG Island microarrays" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, no. 23, 1 December 2001 (2001-12-01), pages 8375-8380, XP002243660 ISSN: 0008-5472 the whole document</p> <p>-----</p>	
A	<p>GITAN RAAD S ET AL: "Methylation-specific oligonucleotide microarray: a new potential for high-throughput methylation analysis" GENOME RESEARCH, COLD SPRING HARBOR LABORATORY PRESS, US, vol. 12, no. 1, January 2002 (2002-01), pages 158-164, XP002208051 ISSN: 1088-9051 the whole document</p> <p>-----</p>	
P,A	<p>WO 03/052135 A (NIMMRICH INKO ; BURGER MATTHIAS (DE); EPIGENOMICS AG (DE); GENC BUELEN) 26 June 2003 (2003-06-26) SEQ ID NO: 28 is 100% identical to SEQ ID NO: 27 of the present application; SEQ ID NO: 648-651 are 100% identical in 17-18 nt overlap with SEQ ID NO: 2005-2008 of the present application.</p> <p>-----</p>	
L	<p>MARTENS J W M ET AL: "Epigenetic signature predicts failure of endocrine therapy in patients with recurrent breast cancer." BREAST CANCER RESEARCH AND TREATMENT, vol. 82, no. Supplement 1, 2003, page S72, XP008030522 26th Annual San Antonio Breast Cancer Symposium; San Antonio, TX, USA; December 03-06, 2003 ISSN: 0167-6806 (ISSN print) the whole document</p> <p>-----</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10881

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-80 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-80 (all partially)

The subject-matter of claims 1-80 as far as it involves STMN1, and SEQ ID NO: 2003-2010.

1.1. claims: 1-80 (all partially)

The subject-matter of claims 1-80 as far as it involves the sequence first mentioned in the claims, namely:

- SEQ ID NO: 27.

Inventions 2-27: claims 1-80 (all partially)

The subject-matter of claims 1-80 as far as it involves:

- SFN, and SEQ ID NO: 2053-2060, for invention 2;
- S100A2, and SEQ ID NO: 1967-1968, 2045-2052, for invention 3;
- TGFBR2, and SEQ ID NO: 2095-2104, for invention 4;
- TP53, and SEQ ID NO: 1987-1986, 2041-2042, for invention 5;
- PTGS2, and SEQ ID NO: 2035-2038, for invention 6;
- FGFR1, and SEQ ID NO: 2031-2034, for invention 7;
- SYK, and SEQ ID NO: 2069-2078, for invention 8;
- PITX2, and SEQ ID NO: 1691-1692, 2025-2030, for invention 9;
- GRIN2D, and SEQ ID NO: 2087-2094, for invention 10;
- PSA, and SEQ ID NO: 1975-1976, 2011-2020, for invention 11;
- CGA, and SEQ ID NO: 1733-1736, 1977-1980, 2021-2024, for invention 12;
- CYP2D6, and SEQ ID NO: 2043-2044, 2127-2134, for invention 13;
- MSMB, and SEQ ID NO: 2039-2040, for invention 14;
- COX7A2L, and SEQ ID NO: 2105-2112, for invention 15;
- VTN, and SEQ ID NO: 2079-2086, for invention 16;
- PRKCD, and SEQ ID NO: 2061-2068, for invention 17;
- ONECUT2, and SEQ ID NO: 2119-2126, for invention 18;
- WBP11, and SEQ ID NO: 2135-2142, for invention 19;
- DAG1, and SEQ ID NO: 2113-2118, for invention 20;
- ERBB2, and SEQ ID NO: 1995-2002, for invention 21;
- TFF1, and SEQ ID NO: 1969-1974, for invention 22;
- TMEFF2, and SEQ ID NO: 1941-1946, for invention 23;
- ESR1, and SEQ ID NO: 1947-1954, for invention 24;
- RASSF1, and SEQ ID NO: 1981-1986, for invention 25;
- PSAT1, for invention 26;
- PCAF, and SEQ ID NO: 1925-1932, 1965-1966, for invention 27.

Inventions 28-159: claims 1-80 (all partially)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ EP 03/10881

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The subject-matter of claims 1-80 as far as it involves:

- SEQ ID NO: 299-300, for inventions 28-29, respectively;
- SEQ ID NO: 325-328, for inventions 30-33, resp.;
- SEQ ID NO: 331-332, for inventions 34-35, resp.;
- SEQ ID NO: 345-346, for inventions 36-37, resp.;
- SEQ ID NO: 381-382, for inventions 38-39, resp.;
- SEQ ID NO: 393-394, for inventions 40-41, resp.;
- SEQ ID NO: 401-402, for inventions 42-43, resp.;
- SEQ ID NO: 411-412, for inventions 44-45, resp.;
- SEQ ID NO: 417-418, for inventions 46-47, resp.;
- SEQ ID NO: 425-430, for inventions 48-53, resp.;
- SEQ ID NO: 443-444, for inventions 54-55, resp.;
- SEQ ID NO: 455-456, for inventions 56-57, resp.;
- SEQ ID NO: 475-476, for inventions 58-59, resp.;
- SEQ ID NO: 487-520, for inventions 60-93, resp.;
- SEQ ID NO: 573-574, for inventions 94-95, resp.;
- SEQ ID NO: 599-602, for inventions 96-99, resp.;
- SEQ ID NO: 605-606, for inventions 100-101, resp.;
- SEQ ID NO: 619-620, for inventions 102-103, resp.;
- SEQ ID NO: 655-656, for inventions 104-105, resp.;
- SEQ ID NO: 667-668, for inventions 106-107, resp.;
- SEQ ID NO: 675-676, for inventions 108-109, resp.;
- SEQ ID NO: 685-686, for inventions 110-111, resp.;
- SEQ ID NO: 691-692, for inventions 112-113, resp.;
- SEQ ID NO: 699-704, for inventions 114-119, resp.;
- SEQ ID NO: 717-718, for inventions 120-121, resp.;
- SEQ ID NO: 729-730, for inventions 122-123, resp.;
- SEQ ID NO: 749-750, for inventions 124-125, resp.;
- SEQ ID NO: 761-794, for inventions 126-159, resp.

Inventions 160-191: claims 1-80 (all partially)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ EP 03/ 10881

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The subject-matter of claims 1-80 as far as it involves:

- SEQ ID NO: 40, for invention 160;
- SEQ ID NO: 122, for invention 161;
- SEQ ID NO: 43, for invention 162;
- SEQ ID NO: 74, for invention 163;
- SEQ ID NO: 127, for invention 164;
- SEQ ID NO: 86, for invention 165;
- SEQ ID NO: 90, for invention 166;
- SEQ ID NO: 128, for invention 167;
- SEQ ID NO: 105, for invention 168;
- SEQ ID NO: 115, for invention 169;
- SEQ ID NO: 121, for invention 170;
- SEQ ID NO: 126, for invention 171;
- SEQ ID NO: 129, for invention 172;
- SEQ ID NO: 125, for invention 173;
- SEQ ID NO: 132, for invention 174;
- SEQ ID NO: 123, for invention 175;
- SEQ ID NO: 131, for invention 176;
- SEQ ID NO: 130, for invention 177;
- SEQ ID NO: 124, for invention 178;
- SEQ ID NO: 68, for invention 179;
- SEQ ID NO: 50, for invention 180;
- SEQ ID NO: 91, for invention 181;
- SEQ ID NO: 92, for invention 182;
- SEQ ID NO: 99, for invention 183;
- SEQ ID NO: 83, for invention 184;
- SEQ ID NO: 41, for invention 185;
- SEQ ID NO: 78, for invention 186;
- SEQ ID NO: 137, for invention 187;
- SEQ ID NO: 133, for invention 188;
- SEQ ID NO: 134, for invention 189;
- SEQ ID NO: 135, for invention 190;
- SEQ ID NO: 136, for invention 191.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Publication
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26-06-2003